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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/619,545	Applicant(s) OLSON ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 7/16/03 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/720200
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/16/03</u> | 6) <input checked="" type="checkbox"/> Other: <u>alignments</u> . |

DETAILED ACTION

Status of the Application

Claims 1-13 are pending.

Applicant's election without traverse of Group I, claims 1-13 directed to a nucleic acid comprising SEQ ID NO: 1-7, vectors, host cells, and kits comprising said nucleic acid, in a communication filed on 2/17/2006 is acknowledged.

Applicant's cancellation of claim 14 in a preliminary amendment filed on 2/17/2006 is acknowledged.

Applicant's preliminary amendment of claim 2 and addition of new claims 11-14 as submitted in a communication filed 8/4/2004 is acknowledged. Upon review of the specification, support for the claims as amended has been found throughout the specification, specifically in page 18, first complete paragraph, page 7, first complete paragraph, and Figure 4.

Applicant's preliminary amendment of the specification deleting hyperlinks present on page 20, as filed on 7/16/2003 is acknowledged.

Claims 1-13 are at issue and are being examined herein.

Specification

1. The title of the invention is objected to for the following reasons. The title recites "nucleotides". As commonly used in the art, the term generally refers to single bases in a nucleic acid molecule. Based on the teachings of the specification, it appears that the specification describes specific nucleic acid molecules having more than one base, i.e., oligonucleotides or polynucleotides. Thus, the term "nucleotides" would not necessarily reflect what is described in the specification.
2. The specification is objected for not complying with sequence rules. While Figures 2-4 display sequences, neither the drawings nor the Brief Description of the Drawings indicate the corresponding

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sequence identifiers. Applicant is required to insert the corresponding sequence identifiers in the Brief Description of the Drawings or amend the drawings to include the sequence identifiers in front of each sequence. See particularly 37 CFR 1.821(d). Appropriate correction is required.

Drawings

3. The drawings are objected to for the following reasons. While Figure 1 shows SEQ ID NO: 1 as the sequence identifier for the displayed sequence, it is noted that the sequence identifier shown does not appear to correspond to what is disclosed in the Sequence Listing. SEQ ID NO: 1 is 15 nucleotides long, whereas the sequence displayed is much longer than 15 nucleotides. Appropriate correction is required in response to this Office action.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the filing date of parent application 09/720,200 is incorrect. According to PTO records, this application was filed on 05/24/2001.

Priority

5. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/090,925 filed on 06/26/1998.

6. SEQ ID NO: 1-7 were first disclosed in provisional application No. 60/090,925 filed on 06/26/1998.

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7. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to SWEDEN 9802294-0 filed on 06/26/1998.

8. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/720,200 filed on 05/24/2001. It is noted that the ADS, transmittal letter and oath/declaration filed on 7/16/2003 disclose a different filing date for US application No. 09/720,200 (12/22/2000). However, as indicated above, PTO records indicate that the filing date of US application No. 09/720,200 is 5/24/2001.

Information Disclosure Statement

9. The information disclosure statement (IDS) submitted on 7/16/2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

10. Claims 1-4, 6-7, 9, 11, 13 are objected to due to the recitation of "nucleotide". The term "nucleotide" as commonly used in the art refers to a single base. However, the claims as written appear to refer to oligonucleotides/polynucleotides (i.e., nucleic acids comprising more than one base). For examination purposes, it will be assumed that the term reads "nucleic acid". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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12. Claims 2, 6, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 2 is indefinite in the recitation of “the nucleotide according to claim 1, wherein said nucleotide appears in a human wild-type alcohol dehydrogenase...gene” for the following reasons. Claim 1 is directed to a nucleic acid encoding a mutant of an alcohol dehydrogenase comprising one or more of SEQ ID NO: 2-7. Claim 2 on the other hand is directed to a nucleic acid encoding a wild-type alcohol dehydrogenase. Thus, it is unclear how the wild-type nucleic acid of claim 2 further limits the genus of mutant nucleic acids of claim 1. For examination purposes, it will be assumed that claim 2 is directed to the mutant of claim 1 wherein said mutant is isolated from humans. Correction is required.

14. Claim 6 is indefinite in the recitation of “stringent conditions” as it is unclear absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. It is noted that while the specification discloses examples of stringent conditions, there is no definition as to what is encompassed by the term such that one of skill in the art could determine which nucleic acids are encompassed by the claim. For examination purposes, it will be assumed that the term reads “any hybridization conditions”. Correction is required.

15. Claim 11 is indefinite in the recitation of “at least about” because it renders the claim vague and confusing. The use of this language is contradictory because the term “about” can be interpreted as “less than” whereas the term “at least” is synonym of “no less than”. For examination purposes, it will be assumed that the term reads “at least”. Correction is required.

Claim Rejections - 35 USC § 101

16. 35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claim 12 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 12 is directed to a human ADH7 sequence comprising one or more SEQ ID NO: 2-7. As known in the art, a nucleotide sequence is a graphical representation of the order in which nucleotides are arranged in a nucleic acid molecule. A graphical representation is neither a product nor a method. Therefore, claim 12 is directed to non-statutory matter.

18. Claims 1-13 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility.

Claims 1-7, 9, 11-13 are directed to nucleic acids comprising one or more of the nucleic acids of SEQ ID NO: 1-7, or variants thereof. Claim 8 is directed to host cells comprising nucleic acids comprising one or more of SEQ ID NO: 2-7. Claim 10 is directed to a kit comprising means to detect at least one of the nucleic acids of SEQ ID NO: 1-7.

Applicants assert that the nucleic acids of SEQ ID NO: 1-7 correspond to small segments of the human alcohol dehydrogenase 7 gene (ADH7) gene which contain mutations which have been labeled M1-M7. It is asserted that mutations M1-M7 are associated with the development of Parkinson's disease (pages 2-3 of the specification). Applicants further indicate that these mutations can be used in the diagnosis, treatment, and/or prevention of Parkinson's disease (page 3, lines 3-6 of the specification).

While Applicants have provided a specific use for the claimed nucleic acids, based upon Applicant's disclosure, the claimed invention does not meet the utility requirement for the following reasons. Applicant's specification discloses that seven polymorphisms were found when screening for the ADH7 gene in 10 patients with confirmed family history of Parkinson's disease (page 23, last paragraph of the specification). These polymorphisms (M1-M7; SEQ ID NO:1-7) were distributed in four different

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alleles (A1-A4, page 24, lines 1-2). The allele frequencies of A1-A4 were determined in 58 patients and 130 controls and it was found that there is an statistical probability that two of the alleles, A1 (M1, M5, M6, and M7) and A3 (M2, M3), can be related to Parkinson's disease (page 25, lines 25-30). There is no evidence linking the presence of these polymorphisms with Parkinson's disease beyond a statistical correlation. Lucentini (The Scientist 18(24):20, 2004) teaches that initial studies showing strong gene-disease associations based on statistical correlations, may provide a wrong association once all the data is carefully reviewed (page 20, first two paragraphs). The instant reference teaches that a couple of studies have shown that when a finding is first published linking a given gene with a complex disease, there is only a one-third chance that studies will reliable confirm the finding (page 20, third paragraph). In the instant case, the specification is completely silent with regard to how these mutations correlate with Parkinson's disease, or how they are responsible for the corresponding symptoms. No information has been provided as to whether these polymorphisms and alleles are applicable to other populations or if the statistical correlation of alleles A1 and A3 is applicable to other populations. In addition, Applicants have not provided evidence that the presence of A1 and A3 in the population tested is sufficient to cause symptoms.

There is no consensus in the current state of the art as to the role of ADH7 gene or its alleles/polymorphisms in Parkinson's disease. Buervenich et al. (Mov. Disord 15 :813-818, September, 2000) teaches that allele A1 has an statistically significant correlation with familial Parkinson's disease (page 816, second column, Discussion). However no determination could be made as to whether the association with A1 is due to the combination of several polymorphisms or one in particular. Moreover, this reference suggests that environmental and/or further genetic factors may still be important in developing symptoms even in individuals carrying the A1 allele. In contrast, Tan et al. (Neuroscience Letters 305 :70-72, 2001) teaches that there is no significant association between the ADH7 A1 allele and an increased risk of Parkinson's disease (page 71, column 1, last paragraph) in a study carried out with

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100 Parkinson's disease patients, 100 disease controls (Huntington's disease and essential tremor), and 100 healthy controls similar in age, gender, and race (Caucasian) as well as 94 healthy controls (Hispanic) (page 70, column 2).

Based on the information provided by Applicant's specification and the current state of the art, it appears that further experimentation is required to determine if the polymorphisms M1-M7 and/or alleles A1-A4 can be used in the diagnosis, treatment, and/or prevention of Parkinson's disease as asserted. In addition, further experimentation would be required to determine whether these polymorphisms are specific to a particular population or if they are also found in other individuals. It is noted that even if polymorphisms M1, M5, M6, M7 could be used in the diagnosis of Parkinson's disease, the claimed polymorphisms M2-M4 would still lack utility because their linkage to this disease has not been established.

Thus, a utility for Parkinson's disease diagnosis, treatment and/or prevention is not considered a "substantial utility" for the claimed nucleic acids because it would require further research to identify or reasonably confirm a "real world" context of use. See e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The instant situation is analogous to the lack of substantial utility examples set forth in MPEP § 2107.01 in that basic research is required to study the properties of the claimed nucleic acids and determine whether they are linked to the disease, how they are linked to the disease, and how they can be used to treat or prevent the disease. Since the instant specification does not disclose a substantial "real world" use or a well-established use for the nucleic acids of SEQ ID NO: 1-7, then the claimed invention (nucleic acids, host cells, vectors and kits) as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

19. Claims 1-13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility

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for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph

20. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 1-4 and 6-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated in MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. In the instant case, the term “mutant alcohol dehydrogenase” has been interpreted as encompassing “any function” in view of the fact that a mutant of an alcohol dehydrogenase does not have to display that enzymatic activity. In view of this interpretation, claims 1, 3, 6-7, 9, 11 are directed to a genus of nucleic acids encoding proteins of any function wherein said nucleic acids (1) comprise one or more of the nucleic acids of SEQ ID NO: 1-7 or SEQ ID NO: 2-7, or (2) are variants which hybridize under any conditions to nucleic acids comprising one or more of SEQ ID NO: 2-7. Similarly, claims 2, 4, 12 and 13 are directed to a genus of human nucleic acids encoding proteins of any function wherein said nucleic acids comprise one or more of the nucleic acids of SEQ ID NO: 1-7 or SEQ ID NO: 2-7. Claim 8 is directed to host cells comprising the genus of nucleic acids of claim 1. Claim 10 is directed to a kit comprising any means to detect at least one of the nucleic acids of SEQ ID NO: 1-7. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no functional limitation recited with regard to the genus of nucleic acids recited, nor there is a functional limitation recited with regard to the polypeptides encoded by the genus of nucleic acids recited. While the specification discloses the nucleic acids of SEQ ID NO: 1-7 as nucleic acids corresponding to small segments of the human ADH7 gene which contain polymorphisms, it fails to provide information as to the function of all the nucleic acids encompassed by the claims, or the biological activity or biological significance of the extremely large number of polypeptides encoded by the claimed nucleic acids as described above. Furthermore, the specification is completely silent with regard to the structural elements required in addition to SEQ ID NO: 1-7 in any nucleic acid, including human nucleic acids, to encode a protein having alcohol dehydrogenase activity. It is worth noting that SEQ ID NO: 1-7 range from 13 to 15 nucleotides in length. With regard to a kit comprising means for detecting at least one of the nucleic acids of SEQ ID NO: 1-7, it is noted that while the specification

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discloses the use of the nucleic acids of SEQ ID NO: 1-7 as probes, the specification is completely silent regarding additional means to detect any of the nucleic acids of SEQ ID NO: 1-7, as encompassed by the claims.

The claims encompass a large genus of nucleic acids which are functionally unrelated. A sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of nucleic acids defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, the recited structural features, "SEQ ID NO: 1-7", "SEQ ID NO: 2-7", "hybridizing under stringent conditions to an isolatedcomprising one or more of SEQ ID NO: 2-7", do not constitute a substantial portion of the genus as the remainder of any nucleic acid comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. As indicated above, SEQ ID NO: 1-7 correspond to nucleic acids having 13-15 nucleotides. The human ADH7 protein is 374 amino acids long. Therefore, it is unlikely that the nucleic acids of SEQ ID NO: 1-7 alone or in combination would encode a protein having alcohol dehydrogenase activity.

While one could argue that the disclosure of the nucleic acids of SEQ ID NO: 1-7 and those of the prior art provide adequate description for all the nucleic acids claimed, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that mutations which result in one conservative amino acid substitution transform a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminate β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since (a) minor structural changes may result in changes affecting function, (b) there

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is no additional information correlating structure with alcohol dehydrogenase activity, and (c) no information has been provided in regard to the additional structural elements required in a polynucleotide encoding an alcohol dehydrogenase, one cannot reasonably conclude that the structures disclosed are representative of the structure of all the nucleic acids as claimed.

Due to the fact that the specification only discloses a few species of the genus, i.e. the nucleic acids of SEQ ID NO: 1-7, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

22. Even if a specific and substantial utility or well established utility is found for the nucleic acids of SEQ ID NO: 1-7, the following rejection applies. Claims 1-4 and 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids consisting of one of SEQ ID NO: 1-7, does not reasonably provide enablement for (1) nucleic acids comprising one or more of SEQ ID NO: 1-7 or SEQ ID NO: 2-7, (2) variants of the nucleic acids of (1), (3) kits comprising any means to detect the nucleic acids of (1), (4) isolated and non-isolated host cells comprising the nucleic acids of (1), or (5) expression vectors comprising the nucleic acids of (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

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The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-4 and 6-13 are so broad as to encompass (1) nucleic acids of any function wherein said nucleic acids (a) comprise one or more of the nucleic acids of SEQ ID NO: 1-7 or SEQ ID NO: 2-7, or (b) are variants which hybridize under any conditions to nucleic acids comprising one or more of SEQ ID NO: 2-7, (2) human nucleic acids of any function wherein said nucleic acids comprise one or more of the nucleic acids of SEQ ID NO: 1-7 or SEQ ID NO: 2-7, (3) host cells comprising the nucleic acids of (1), and (4) a kit comprising any means to detect at least one of the nucleic acids of SEQ ID NO: 1-7. See Claim Rejections under 35 USC 112, first paragraph, written description, and 35 USC 112, second paragraph for claim interpretation. The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids of unknown function and virtually unknown structure recited in the claims. It is reiterated herein that the nucleic acids of SEQ ID NO: 1-7 are 13-15 nucleotides in length. In the instant case, the specification enables the nucleic acids of SEQ ID NO: 1-7.

With regard to claim 8, it is noted that the specification contemplates the nucleic acids of the invention to be used for the generation of transgenic animals (page 18, lines 4-24) and for *in vivo* expression and gene therapy (page 19, lines 5-11). Therefore, in its the broadest reasonable interpretation, claim 8 is directed not only to isolated host cells but also to host cells within a transgenic multicellular organism (i.e., non-isolated). The enablement provided is not commensurate in scope with the claim due to the extremely large number of transgenic multicellular organisms comprising the cells encompassed by the claim which the specification fails to teach how to generate or how to use. In the instant case, the specification enables an isolated host cell comprising a vector which contains one or more of the nucleic acids of SEQ ID NO: 1-7.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the nucleic acids of SEQ ID NO: 1-7 as working examples. However, the specification fails to provide any clue as to (1) all the functions associated with the nucleic acids encompassed by the claims, or (2) the structural elements required in any nucleic acid encoding a protein having alcohol dehydrogenase activity. No correlation between structure and alcohol dehydrogenase activity, or any other activity, has been presented. As previously indicated, it is unlikely that the nucleic acids of SEQ ID NO: 1-7 alone or in combination would encode a protein having alcohol dehydrogenase activity in view of the fact that an alcohol dehydrogenase is expected to be coded by a longer polynucleotide.

With regard to claim 8, while the specification discloses that the nucleic acids of the invention can be used to transform host cells for generation of transgenic animals, for *in vivo* expression and for gene therapy, there are no working examples or specific methods disclosed showing a transgenic multicellular organism capable of expressing the claimed nucleic acids. Also, there are no working examples or specific methods disclosed showing how to deliver the claimed genus of nucleic acids to human tissues such that the claimed nucleic acids can be expressed.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, even if it is assumed that the claims are limited functionally to alcohol dehydrogenases, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a polypeptide having alcohol dehydrogenase activity. In addition, the art does not provide any teaching or guidance as to (1) which nucleotides in the nucleic acids of SEQ ID NO: 1-7 can be modified and which ones are conserved such that one of skill in the art can make variants as recited encoding polypeptides with alcohol dehydrogenase activity, and (2) the general

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tolerance of alcohol dehydrogenases to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

With regard to transgenic multicellular organisms, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549, right column, third paragraph). Furthermore, Mullins et al. (Hypertension 22(4):630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631, left column, first paragraph, last sentence). Also, Mullins et al. (J. Clin. Invest. 97(7):1557-1560, 1996) teach that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for

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the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (page 1559, Summary). Wigley et al. (Reprod. Fert. Dev. 6:585-588, 1994) indicate that transgenesis by microinjection has a number of limitations including random integration in the genome and integration of transgenes in multiple copies at one site such that expression level is not proportional to transgene copy number (page 585, Introduction). Cameron (Molecular Biotechnology 7:253-265, 1997) teaches that well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (page 256, left column, last three lines, right column, first three lines). According to Cameron, transgene expression with different transgenic lines produced with the same constructs is unpredictable and expression levels do not correlate with the number of transgene copies integrated, thus indicating the influence of the integration site on the expression pattern (page 256, right column, lines 3-13).

In regard to DNA delivery and expression in human tissues, the art teaches the high unpredictability of delivering DNA to human tissues and achieving the desired expression. For example, Phillips (J. Pharm. Pharmacology 53:1169-1174, 2001) teaches that the major challenges in gene therapy have been delivery of DNA to target cells and duration of expression (Abstract). According to Phillips, the problem regarding gene therapy is twofold in that (1) a system must be design to deliver DNA to a specific target while preventing degradation within the body, and (2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for a determined amount of time (page 1170, left column, lines 7-15). Gardlik et al. (Med. Sci. Monit. 11(4):RA110-121, 2005) teach that (1) while there are a number of methods known for delivery of DNA, there is no clear ideal delivery system (RA119, last paragraph), and (2) the main problem in gene therapy lies in the secure and efficient delivery of genes into target cells and tissues (RA110, Summary).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a nucleic acid were

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known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for the extremely large number of nucleic acids encompassed by the claims to determine (1) the function of all the nucleic acids encompassed by the claims such that a use can be found for those nucleic acids, or (2) which nucleic acids encode polypeptides having alcohol dehydrogenase activity.

Furthermore, it is not routine in the art to isolate/create any nucleic acid encoding a protein with the desired activity without any knowledge as to the structural features which would correlate with that activity. In the absence of (1) a rational and predictable scheme for modifying (i.e., adding, deleting, and/or substituting) any nucleotide in the nucleic acids of SEQ ID NO: 1-7, such that the resulting variant would encode a protein which has alcohol dehydrogenase activity, and/or (2) a correlation between structure and alcohol dehydrogenase activity, one of skill in the art would have to test an essentially infinite number of polynucleotides to determine which ones encode proteins having alcohol dehydrogenase activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims. In addition, given the teachings of the art regarding the differences in expression of a transgene in different species, the limitations regarding the integration and expression of a transgene, the unpredictability of delivering and expressing DNA in human tissues, and in view of the lack of guidance provided by the specification, it would have required undue experimentation to engineer any transgenic multicellular organism, or cells thereof, as claimed.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to (a) structural

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changes and their effect on function, (b) generation of transgenic multicellular organisms, and (c) delivery and expression of DNA in human tissues, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 1-3, 6-8, 11-12 are rejected under 35 U.S.C. 102(a) as being anticipated by (1) Sage-Ono et al. (Plant Physiol. 116:1479-1485, April, 1998; GenBank accession number D85101, May 2, 1998), (2) Carson et al. (GenBank AA080645, October 28, 1997), and (3) NCI-CGAP (GenBank accession number AA906249, May 19, 1998).

Sage-Ono et al. disclose mRNA which encodes for a leaf protein from *Pharbitis nil* which comprises all of SEQ ID NO: 2 as well as cloning vectors and host cells (page 1480, right column, last paragraph-page 1481, left column, lines 1-3). See attached alignment provided for visualization purposes.

Carson et al. disclose an EST of sugarcane cDNA from leaf roll tissue which comprises all of SEQ ID NO: 4, cloning vectors and host cells comprising said vectors (see GenBank entry under Features/source/clone and Features/source/note). See attached alignment provided for visualization purposes.

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NCI-CGAP discloses a human EST which comprises all of SEQ ID NO: 7, cloning vectors and host cells comprising said vectors (see GenBank entry under Features/source/lab host and Features/source//note). See attached alignment provided for visualization purposes.

Claim 1 as interpreted is directed to a nucleic acid comprising one or more of SEQ ID NO: 2-7. Claim 2 as interpreted is directed to the nucleic acid of claim 1 wherein the nucleic acid is a human nucleic acid. Claim 3 is directed to a nucleic acid comprising SEQ ID NO: 2. Claim 6 is directed to a nucleic acid which hybridizes under any conditions to the nucleic acid of claim 1. Claim 7 is directed to a vector comprising the nucleic acid of claim 1. Claim 8 is directed to a host cell comprising the vector of claim 7. Claim 11 is directed to a nucleic acid which hybridizes under a wide range of conditions to a nucleic acid comprising one or more of SEQ ID NO: 2-7. Claim 12 is directed to a human nucleic acid comprising one or more of SEQ ID NO: 2-7. See Claim Rejections under 35 USC 112, first paragraph, written description, and 35 USC 112, second paragraph for claim interpretation. Therefore, the teachings of Sage-Ono et al. anticipate claims 1,3, 6-8, 11 as written, the teachings of Carson et al. anticipate claims 1, 6-8, and 11 as written, and the teachings of NCI-CGAP anticipate claims 1-2, 6-8, 11-12 as written.

25. Claims 1-2, 6-8, 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by (1) Zgombic-Knight et al. (J. Biol. Chem. 270:4305-4311, 1995), (2) Yokoyama et al. (Biochemical and Biophysical Research Communications 212(3):875-878, 1995; GenBank accession number L39009, March 7, 1996), (3) Glass et al. (GenBank accession number U30500, September 1, 1995), (4) King et al. (GenBank accession number L41145, April 1, 1995), and (5) Mathews et al. (American Journal of Physiology 268:C1207-C1214, 1995; GenBank accession number U17249, September 27, 1995).

Zgombic-Knight et al. disclose the complete genomic structure of the ADH7 gene which encodes the human class IV alcohol dehydrogenase (Figure 2) as well as cloning vectors and host cells comprising said vectors (page 4306, right column, Isolation of genomic DNA clones encoding human class IV ADH).

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Zgombic-Knight et al., as acknowledged by Applicants (page 4, lines 18-21 of the specification), discloses SEQ ID NO: 1 (M1; see Figure 2, page 4308 of Zgombic-Knight et al.; see also nucleotides –102 to –88 in Figure 1 of Applicant's specification) as being part of the wild type sequence.

Yokoyama et al. disclose a polynucleotide which corresponds to the 5' flanking region of the human ADH7 gene and comprises all of SEQ ID NO: 1. See attached alignment. Yokoyama et al. also teaches cloning vectors and host cells comprising said vectors (page 876, Molecular cloning and sequencing of a Caucasian ADH 7 gene). See attached alignment provided for visualization purposes.

Glass et al. disclose a polynucleotide encoding a Sicilian sandfly fever virus glycoprotein precursor which comprises all of SEQ ID NO: 3. See attached alignment provided for visualization purposes.

King et al. disclose a polynucleotide encoding a mouse bone morphogenetic protein which comprises all of SEQ ID NO: 5. See attached alignment provided for visualization purposes.

Mathews et al. discloses mRNA encoding a frog ATPase alpha-subunit which comprises all of SEQ ID NO: 6, cloning vectors and host cells comprising said vectors (page C1207, right column, last sentence-page C1209, right column, lines 1-12). See attached alignment provided for visualization purposes.

Claim 1 is directed to a nucleic acid comprising one or more of SEQ ID NO: 2-7. Claim 2 as interpreted is directed to the nucleic acid of claim 1 wherein the nucleic acid is a human nucleic acid. Claim 3 is directed to a nucleic acid comprising SEQ ID NO: 2. Claim 6 is directed to a nucleic acid which hybridizes under any conditions to the nucleic acid of claim 1. Claim 7 is directed to a vector comprising the nucleic acid of claim 1. Claim 8 is directed to a host cell comprising the vector of claim 7. Claim 11 is directed to a nucleic acid which hybridizes under a wide range of conditions to a nucleic acid comprising one or more of SEQ ID NO: 2-7. Claim 12 is directed to a human nucleic acid comprising one or more of SEQ ID NO: 2-7. See Claim Rejections under 35 USC 112, first paragraph, written

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description, and 35 USC 112, second paragraph for claim interpretation. Therefore, (1) the nucleic acid of Zgombic-Knight et al. anticipates claims 6 and 11 since it would hybridize to the nucleic acids of SEQ ID NO: 2-7, as evidenced by the teachings of the specification where it is disclosed that the nucleic acids of SEQ ID NO: 2-7 are fragments of the wild type nucleic acid of Zgombic-Knight et al. where single modifications have been made, (2) the teachings of Yokoyama et al. anticipate claims 6, 11, (3) the teachings of Glass et al. and King et al. anticipate claims 1, 6, 11, and (4) the teachings of Mathews et al. anticipate claims 1, 6-8, 11 as written.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over (1) Glass et al. (GenBank accession number U30500, September 1, 1995), and (2) King et al. (GenBank accession number L41145, April 1, 1995). The teachings of Glass et al. and King et al. have been discussed above. Neither Glass et al. nor King et al. teach vectors or host cells.

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Claim 7 is directed to a vector comprising the nucleic acid of claim 1 as described above. Claim 8 is directed to a host cell comprising the vector of claim 7.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector comprising the nucleic acids of Glass et al. or King et al. and transform a commonly used host cell with said expression vector for recombinant protein production. A person of ordinary skill in the art is motivated to construct such a vector and express the proteins encoded by said nucleic acids for the benefit of producing large amounts of protein for further characterization studies. One of ordinary skill in the art has a reasonable expectation of success at making the vector and transforming a commonly used host cell for expressing the nucleic acids of Glass et al. or King et al. in view of the fact that recombinant protein expression where an expression vector is inserted in a commonly used host cell is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

29. Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over (1) Zgombic-Knight et al. (J. Biol. Chem. 270:4305-4311, 1995), (2) Yokoyama et al. (Biochemical and Biophysical Research Communications 212(3):875-878, 1995; GenBank accession number L39009, March 7, 1996), (3) Glass et al. (GenBank accession number U30500, September 1, 1995), (4) King et al. (GenBank accession number L41145, April 1, 1995), (5) Mathews et al. (American Journal of Physiology 268:C1207-C1214, 1995; GenBank accession number U17249, September 27, 1995), (6) Sage-Ono et al. (Plant Physiol. 116:1479-1485, April, 1998; GenBank accession number D85101, May 2, 1998), (7) Carson et al. (GenBank AA080645, October 28, 1997), and (8) NCI-CGAP (GenBank accession number AA906249, May 19, 1998). The teachings of the instant references have been discussed above. None of these

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references teach a kit comprising (a) a nucleic acid which can detect one of the nucleic acids of SEQ ID NO: 1-7 or (b) a nucleic acid comprising one or more of SEQ ID NO: 2-7.

Claim 9 is directed to a kit comprising the nucleic acid of claim 1, as discussed above. Claim 10 is directed in part to a kit comprising nucleic acids which would detect the nucleic acids of SEQ ID NO: 1-7.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a kit comprising the nucleic acids of Zgombic-Knight et al., Yokoyama et al., Glass et al., King et al., Mathews et al., Carson et al., Sage-Ono et al., or NCI-CGAP. A person of ordinary skill in the art is motivated to make such kit for the benefit of providing in one package all the necessary reagents to detect nucleic acids having similar or identical structure. One of ordinary skill in the art has a reasonable expectation of success at making the kit with the nucleic acids of Zgombic-Knight et al., Yokoyama et al., Glass et al., King et al., Mathews et al., Carson et al., Sage-Ono et al., or NCI-CGAP in view of the fact that assembly of kits comprising nucleic acid probes and the necessary reagents for detection is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

30. No claim is in condition for allowance.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 1, 2006